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ORIGINAL RESEARCH

Identification of Patients with New-Onset Heart Failure and Reduced Ejection Fraction in Danish Administrative Registers

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Background: In Danish administrative registers, ejection fraction (EF) is not recorded, which is a considerable limitation for correct subclassification of patients with heart failure (HF). We hypothesized that a diagnosis of HF combined with the recorded prescription of both renin-angiotensin system (RAS) inhibitors and beta- blockers (*RASi+BB*) within 120 days could identify patients with HF and reduced ejection fraction (EF ≤40%) (HFrEF).

Methods: On two sites, we identified all patients with a first-time registration of HF as primary hospital discharge diagnosis (ICD-10: I50) between June 1, 2016, and May 31, 2018 in inpatient or outpatient settings. Patients were included if they survived the initial 120 days after discharge. Reviewing patient records, we identified patients with HFrEF, based on EF ≤ 40% and reported HF symptoms. We registered the use of *RASi+BB* at 120 days and calculated sensitivity, specificity and predictive values.

Results: A total of 704 consecutive patients with a primary diagnosis of HF were included, of whom 541 (77%) fulfilled the HFrEF criteria. Patients with HFrEF confirmed from patient records were younger (median age 73 compared to 79 years) and less frequently women (31% compared to 56%) compared to non-HFrEF patients. At baseline, 24 (4%) of HFrEF patients were treated with *RASi+BB* compared to 22 (14%) of non-HFrEF patients. At 120 days, 460 (85%) of HFrEF patients received *RASi+BB* as compared to 25 (15%) of non-HFrEF patients. This resulted in a positive predictive value of 95%, sensitivity of 85% and specificity of 85%.

Conclusion: In Denmark, the ICD-10 HF diagnosis combined with recorded *RASi+BB* treatment by 120 days after discharge has high positive predictive value and can accurately be used to identify patients with HFrEF.

Keywords: heart failure, reduced ejection fraction, register data, validation

Introduction

Danish administrative registers have a high level of consistency and completeness of data, and are, therefore, widely used for epidemiological studies. Due to a unique personal identification number given to all Danish citizens at birth or immigration, individuals can be identified in different registers and across different geographical regions within Denmark.[1,2] Identification of patients with heart failure (HF), based on international classification of disease (ICD-10) codes has previously been evaluated in the Danish registers documenting a relatively high positive predictive value (PPV) ranging from 81% to 100% depending on which method was used for validation.[3–5] However, the ICD-10 system does not distinguish between HF with

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reduced (HFrEF) and preserved (HFpEF) ejection fraction (EF), as the ICD-10 code for HF (I50) comprises both.

The network of Danish heart failure clinics ensures that the majority of Danish citizens who are diagnosed with HFrEF are offered consultations in a dedicated HF clinic with a focus on uptitration of guideline-directed medical therapy and patient education in self-care, usually over a period of 4 to 6 months.[6,7] Since renin-angiotensin system inhibitors (RASi) and beta-blockers (BB) are recommended for all patients with HFrEF, if tolerated,[8] we hypothesized that patients with HFrEF who survived the initial 120 days (~4 months) after receiving the diagnosis, could be identified based on the ICD-10 discharge code and filled prescriptions of *RASi+BB* within that time period.

Methods

This study was a part of a quality assurance project, with the purpose of evaluating the proportion of patients with HF alive after 120 days, who had initiated RASi and/or BB within 90 and 120 days, respectively. In the National Patient Register, we identified all patients who received a first-time HF diagnosis (ICD-10: I50) as a primary discharge diagnosis on two sites, Gentofte University Hospital and Herlev University Hospital, within a two-year period from June 1, 2016 through May 31, 2018. Patients who survived the initial 120 days after the time of diagnosis were included. Based on the review of patient records, patients were considered to have HFrEF if symptoms of HF were reported and an EF $\leq$ 40% was documented in the chart. If several echocardiograms had been performed, either during the hospitalization or in the outpatient clinic, the first available measurement of EF was used to define HFrEF status in accordance with clinical practice. Symptoms of HF were shortness of breath, reduced exercise tolerance, fatigue and/or ankle swelling. Use of RASi (including angiotensin-converting enzyme inhibitors [ACEi] and angiotensin receptor blockers [ARB]) and BB was assessed at baseline (treatment initiated before the time of diagnosis) and at 120 days after diagnosis.

Statistical Methods

Baseline characteristics were presented as absolute numbers and proportions for categorical variables and medians and inter-quartile ranges (IQR) for continuous variables. Variables with missing data were presented as proportions and IQR relative to the group of patients with available data. Based on the ICD-10 discharge coding diagnosis for heart failure (I50) and status of *RASi+BB* at 120 days, we calculated sensitivity, specificity and predictive values for HFrEF.

Ethical Considerations

Register studies and patient record review studies do not require ethical approval in Denmark. The present quality assurance project was approved by the hospital direction (workzone number: 19,000,557). Patient data was anonymized immediately, and individuals included in the analyses could not be identified at a later point.

Results

Study Population

A total of 704 patients had a first-time HF diagnosis between June 1, 2016 and May 31, 2018 and were still alive after 120 days. Of those, 541 (76.8%) had well-described HFrEF. Less information was available for the non-HFrEF group (n=163) and for 43 (26.4%) patients an echocardiography had not been performed. Of the patients with HFrEF, 503 (93.0%) attended the HF clinic compared to only 21 (12.9%) of the non-HFrEF patients. Baseline characteristics are listed in Table 1. Comorbidity data was missing for 101 individuals – none of whom attended the HF clinic.

Use of RASi and BB

At baseline, 24 (4.4%) patients with HFrEF and 22 (13.5%) non-HFrEF patients were treated with *RASi+BB*. After 120 days, 460 (85.0%) patients with HFrEF and 25 (15.3%) non-HFrEF patients were taking *RASi+BB*. For patients with HFrEF who attended a HF clinic, 444 (88.3%) were receiving *RASi+BB* therapy after 120 days, as illustrated in Table 2. Identifying patients with HFrEF among patients discharged with an I50 diagnosis, and based on treatment with *RASi+BB* was associated with a PPV of 94.8% as shown in Figure 1 and Table 3. This, however, came with a sensitivity of 85.0%. An even higher PPV of 99.1% could be obtained by selecting patients who were naïve to either RASi or BB at the time of diagnosis. In this case, the sensitivity was 80.1%.

Patients with HFrEF and Without RASi and BB

According to patient records, reasons for not initiating RASi and/or BB therapy in patients with HFrEF were most often low blood pressure, low heart rate (BB), or reduced renal function (RASi). However, comparing

Table 1 Baseline Characteristics. Count/Median (Percentage, Inter-Quartile Range) [Data Available in % Individuals]

	HFrEF (n=541)	Non-HFrEF (n=163)
Female sex	169 (31.2) [100.0]	91 (55.8) [100.0]
Age	73.2 (63.9, 80.7) [100.0]	79.2 (71.8, 85.5) [100.0]
Hospitalization with HF symptoms	421 (77.8) [100.0]	83 (50.9) [97.5]
Attending heart failure clinic	503 (93.0) [100.0]	21 (12.9) [100.0]
Ischemic heart disease	167 (30.9) [100.0]	16 (25.8) [38.0]
Diabetes	81 (15.2) [100.0]	16 (25.8) [38.0]
Atrial fibrillation/flutter	224 (41.4) [100.0]	31 (50.0) [38.0]
Claudication	12 (2.2) [100.0]	<3 (<4.8) [38.0]
Stroke	52 (9.6) [100.0]	9 (14.5) [38.0]
Chronic obstructive pulmonary disease	70 (12.9) [100.0]	12 (19.4) [38.0]
Medical therapy		
Renin angiotensin system inhibitors	108 (20.0%) [100.0]	53 (32.5%) [100.0]
Beta-blocker	85 (15.7%) [100.0]	56 (34.4%) [100.0]
Renin angiotensin system inhibitors and beta-blocker	24 (4.4%) [100.0]	22 (13.5%) [100.0]
Clinical measurements		
Left ventricular ejection fraction	30 (20, 37) [100.0]	55 (47, 60) [73.6]
Increased level of creatinine	99 (19.3%) [95.0]	10 (25.0%) [24.5]
Systolic blood pressure <100mmHg	18 (3.5%) [94.6]	<3 (2.9%) [21.5]
Heart rate <60 beats per minute	56 (11.3%) [91.3]	3 (9.4%) [19.6]
NTproBNP	1510 (619, 3460) [79.7]	1375 (224, 3483) [13.5]

Abbreviations: HFrEF, heart failure with reduced ejection fraction; HF, heart failure.

Table 2 Frequency of RASi and Beta-Blocker Therapy After HF Diagnosis

	Baseline	120 Days
HFrEF (n=541)		
RASi	108 (20.0)	496 (91.7)
Beta-blocker	85 (15.7)	492 (90.9)
RASi + beta-blocker	24 (4.4)	460 (85.0)
Neither	372 (68.8)	13 (2.4)
HFrEF in HF clinic (n=503)		
RASi	94 (18.7)	473 (94.0)
Beta-blocker	69 (13.7)	469 (93.2)
RASi + beta-blocker	19 (3.8)	444 (88.3)
Neither	359 (71.4)	5 (1.2)
Non-HFrEF (n=163)		
RASi	53 (32.5)	59 (36.2)
Beta-blocker	56 (34.4)	63 (38.7)
RASi + beta-blocker	22 (13.5)	25 (15.3)
Neither	76 (46.6)	66 (40.5)
Non-HFrEF in HF clinic (n=21)		
RASi	8 (38.1)	9 (42.9)
Beta-blocker	<3 (<7.0)	3 (7.0)
RASi + beta-blocker	<3 (<7.0)	<3 (<7.0)
Neither	11 (52.4)	10 (47.6)

baseline characteristics of patients with and without *RASi+BB* at day 120 revealed no significant differences in presence on these three parameters. Patients without *RASi+BB* were older with a median age of 79.7 (71.4, 87.0) years.

Patients Without Echocardiography

Patients without a documented echocardiography, n=43, were classified as non-HFrEF. Among these patients, 6 (14%) were taking *RASI+BB* at 120 days – the same 6 patients were treated with *RASi+BB* at baseline.

Discussion

This study demonstrates that a population of patients with HFrEF can be identified from the Danish registers based on diagnosis and medical prescriptions with a PPV of 95%. The ability to accurately identify patients with HFrEF is important for the design and validity of future epidemiological studies.

To our knowledge, this study is the first to evaluate the identification of a specific HF subgroup in the Danish administrative registers. The PPV of the HF diagnosis has previously been evaluated with different approaches.

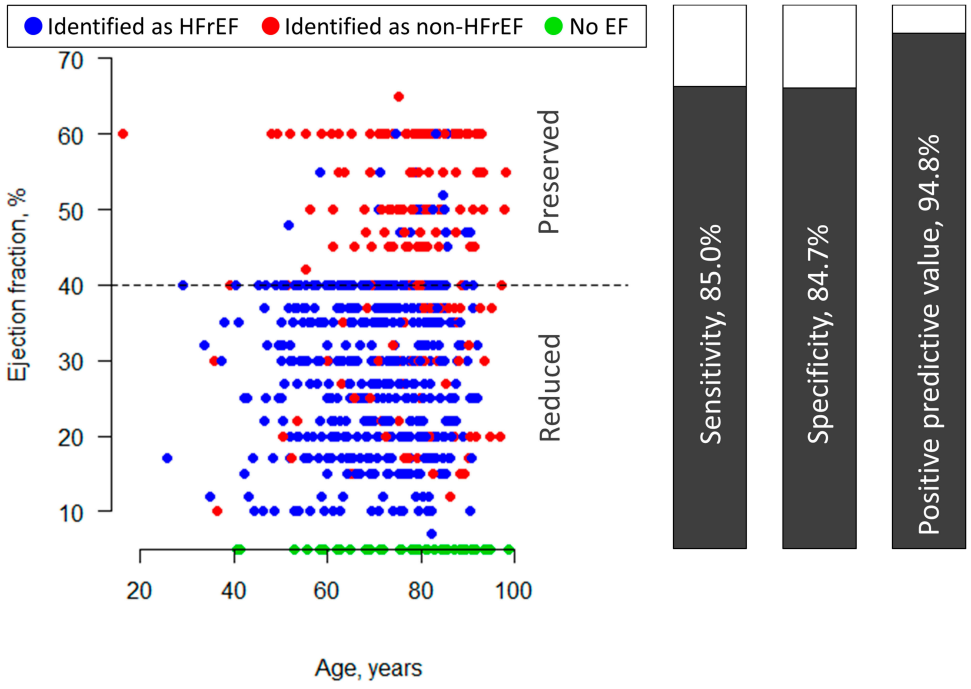

Figure 1 Left side: Patients identified as HFrEF (blue) and non-HFrEF (red) plotted with age and EF. Patients without information on EF (green) plotted along the age-axis. Right side: Sensitivity, specificity and positive predictive value of confirmed HFrEF by using diagnosis code and RASi+BB at 120 days.
Abbreviations: EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction; RASi, renin-angiotensin-system inhibitor; BB, beta-blocker.

In a study using discharge summaries to verify the diagnosis, the PPV was found to be 100% for 50 patients reviewed.[5] This method solely relied on the opinion of the discharging physician and it is unknown whether diagnostic tests were performed. This is a valuable method to ensure that the National Patients Register is reflecting the diagnoses given at discharge, but it is less valuable for determining whether the diagnostic criteria were met in the clinical situation. Therefore, important additional data were obtained, when 3201 hospitalized patients were evaluated with a clinical examination and echocardiography in another previous study. In this study, the PPV was found to be 81%, as 30 patients out of 156 with a registered diagnosis, did not have HF according to the European Society of Cardiology criteria.[3] Moreover, this study revealed a low sensitivity of 29% (39% for HFrEF) among all patients hospitalized. The study included patients admitted to any department and did not consider prior diagnoses, which may explain the low sensitivity, as the HF diagnosis patient with well-known and well-treated HF may not have been recorded if the patient was admitted for non-cardiovascular comorbidity. The sensitivity of the register-based approach documented in the present study is not comparable to the study by Kumler, as the current study is derived from a population with registered HF. Consequently, the results of the current study reflect the proportion of true HFrEF among patients with a HF diagnosis identified using our definition. The main purpose, however, was to estimate the PPV of HFrEF, and we found that it was surprisingly high even when only using the diagnosis (541/704) = 77%. When adding RASi+BB use to the definition, 219 patients were redefined as non-HFrEF, of whom, at least 81 had HFrEF. In the group of non-HFrEF patients, the description of symptoms of HF in the medical records was less detailed, and NTproBNP was only measured in a few patients. Hence, it was, therefore, difficult to determine the proportion of true HFpEF. Due to a lack of echocardiography for some patients, we cannot rule out that they had HFrEF. If this were the case, for all these

Table 3 Sensitivity, Specificity and Predictive Values of Confirmed HFrEF by Using Diagnosis Code and RASi+BB at 120 Days

	Non-HFrEF	HFrEF	Total
Not RASi and beta-blocker	138	81	219
RASi and beta-blocker	25	460	485
Total	163	541	704

Notes: Sensitivity, 460/541 = 85.0%. Specificity, 138/163 = 84.7%. Positive predictive value: 460/485 = 94.8%. Negative predictive value: 138/219 = 63.0%.

patients it would slightly increase the PPV to 96%, while reducing the sensitivity to 80%.

The proportion of HFpEF was low, even if all patients categorized as non-HFrEF had true HFpEF. This proportion has varied in the literature depending on definition, method and clinical settings. From the European Society of Cardiology HF Long-Term Registry, it has been reported that a third of the patients with chronic HF had an EF >40%.[9] In the hospital, HFpEF may be underreported in the presence of comorbidity, and it is unknown how many patients are merely treated symptomatically with diuretic therapy without having a registered HF diagnosis. In a recent Danish study examining patients with risk factors for HF but without known HF, 37% had an abnormal echocardiography but no symptoms of HF (stage B HF), while 18% had abnormal echocardiography and symptoms of HF (stage C HF).[10] Among those with unrecognized HF (stage C) 94% had an EF>40%, which supports the hypothesis of HFpEF being underdiagnosed. Further, even recognized HFpEF may have low registration rates in Denmark due to our public tax-paid health care system, where registration of a diagnosis is not associated with the same financial or competitive benefits for the hospitals as in other countries. This does not affect the validity of the data presented, but it may affect the generalizability of the proposed method to other countries; the PPV will be lower in populations with a higher proportion of HFpEF. Therefore, this method should be tested in other cohorts before being applied in settings different from the Danish.

A considerable part of the cohort did not receive *RASi+BB* by 120 days. The reported rationale of avoiding/postponing initiation of RASi was often a high level of creatinine, while BB was often avoided/postponed due to low blood pressure or low heart rate. However, we observed no significant difference in the frequency of low blood pressure, heart rate, or high level of creatinine at baseline between patients with and without *RASi+BB* at day 120. It is likely that the treatment decision is partly based on the patients' clinical appearance, and parameters such as a low cardiac output state may indicate full up-titration of RASi before initiation of (and therefore postponing) BB. Another explanation could be that patients who experienced an early readmission had a delay in otherwise planned interventions and up-titration of medical therapy. However, early readmission rates are low in Denmark, so this should only apply to a minority of the patients.[11] Noticeably, only 2% of the patients with HFrEF initiated neither RASi nor BB. Further, it is unknown how many of these patients initiated *RASi+BB* at a later point after 120 days.

Strengths and Limitations

The Danish health care system is highly homogenous in terms of diagnostic approaches, treatment strategies and quality of care, which is a major strength for a study as the present, relying on nationwide generalizability. The two hospitals included were both university hospitals, but represented both invasive and non-invasive cardiology departments.

Defining HFrEF in the Danish registers using the I50 code and post-discharge initiation of *RASi+BB* within a certain period inherently results in the exclusion of patients dying within this period, which introduces selection bias towards the younger and less frail patients. Unfortunately, we did not have data regarding these excluded patients; however, in previous work on data from the nationwide registers, 20% of 172,580 patients diagnosed with HF from 2000 to 2012 died within 120 days – including those who died during the initial hospitalization.[12] The distribution of early death between patients with and without HFrEF is unknown. Further, the present analyses showed a loss of 15% of the patients with HFrEF surviving the initial 120 days, using the proposed method. These patients were older than the included patients were and, likely, more frail. This should be kept in mind when applying the method in future epidemiological research, but it may be less important for studies concerning patients with chronic HF.

We acknowledge that estimating EF is susceptible to inter- and intra-observer variability and patients with an EF close to 40% could be misclassified. However, this reflects the daily clinical practice and is not considered a limitation for the purpose of this study.

Conclusions

In Danish administrative registers, the combination of a HF and initiation of RASi as well as BB by 120 days after diagnosis defines HFrEF with a PPV of 95%. Despite a sensitivity of 85%, using this method for register studies is reasonable.

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Disclosure

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